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Title: Skeletal changes during catch-up growth - suggestions from a rat model

Date: 2001

Originally published in: An abstract appeared in *Annals of Human Biology*

Example citation: Lewis, S. J. (2001). Skeletal changes during catch-up growth - suggestions from a rat model. *Annals of Human Biology*, 28, 354

Version of item: Presentation

Available at: <http://hdl.handle.net/10034/56673>

Skeletal changes during catch-up growth

- suggestions from a rat model

Stephen Lewis†

Abstract

The removal of a growth limiting influence, such as undernutrition, is frequently followed by a period of growth at a rate greater than normally expected for chronological age. This, so called 'catch-up growth', tends to return affected individuals to their original growth trajectory. How catch-up growth is controlled or regulated remains unclear.

Histological studies of the proximal tibial growth plate in rats which had been undernourished by half-feeding between the 56th and 70th days (post partum) showed them to be thinner than those of controls. Upon inspection, the chondrocytes also appeared to be flatter in profile and less numerous. However, during the catch-up period, when food was again allowed ad libitum, previously undernourished rats showed wider growth plates with rounder and more numerous chondrocytes than controls. It was noted that such changes were similar to those that accompany sectioning of the periosteum and the release of growth restraint that results.

A study of the flexibility of the sacro-iliac joint in the same animals suggested that it was less flexible following undernutrition but more so during the catch-up period, by comparison with controls. This was in contrast to a progressive loss of flexibility shown by controls during the same period and would appear to result from changes in the characteristics of the fibrous connective tissues associated with the joint.

If this reflects a more generalized change in such connective tissues, but particularly the periosteum, ligaments and joint capsules, this may represent a means whereby skeletal growth rate during the catch-up period may be influenced in a co-ordinated manner.

Introduction

Normal growth is a very orderly process. So regular is it that Tanner (1981) could state that the "rate of growth is one of the best indicators of a child's general health". A variety of factors can upset this orderly process, however, causing deviations from a child's projected growth trajectory and a deficiency in expected size. Amongst these factors is undernutrition which acts to cause a depression in the age specific growth rate. When adverse factors, such as undernutrition, are removed, growth rate increases again but often to levels which exceed those expected for a child's chronological age. In such cases, any deficiency in size which may have resulted from growth impairment may be abolished. Thus, such a period of accelerated growth is often called 'catch-up growth'. What causes or regulates catch-up growth remains unclear - as indeed does the mechanism for the slowing of the rate of growth that precedes it. 'Catch-up growth' is not a good term because it tends to presuppose, or at least imply, a deliberate response on the part of the organism to actively overcome size deficits resulting from growth retardation. It is quite possible that the mechanism responsible for catch-up growth makes no deliberate attempt to restore lost growth but only appears to do so. Given the effects of undernutrition on growth, it can also be used as an experimental technique in the study of growth as it can be imposed under controlled conditions. The following investigation is a preliminary experiment, using sometimes rather unsophisticated equipment and techniques, designed to explore a 'connective tissue hypothesis' accounting for both growth retardation and catch-up growth.

Materials and Methods

A group of male Wistar rats was raised under standard conditions (8 per litter until weaning, 2 per cage thereafter, in a light/dark cycle of 12hr/12hr and 20-22°C) until the 56th day *post partum* when they were divided into a control group - which received food and water *ad libitum* - and an experimental group (caged individually) - which received half the amount of food consumed by the control group, until the 70th day *post partum*. At intervals, animals were sacrificed and the left knee dissected and prepared for histological examination of the proximal tibial epiphyseal growth plate and the pelvis, with a section of the vertebral column (including part of the tail), dissected and prepared for studies of sacro-iliac joint flexion.

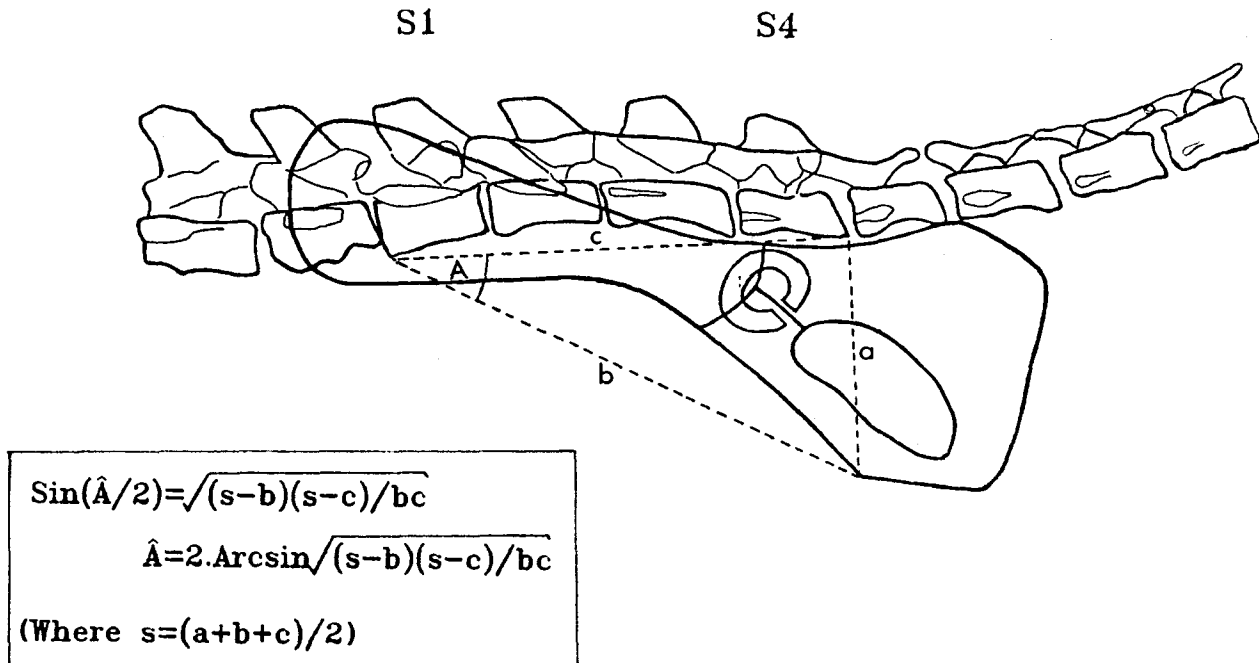
The thickness of the growth plate was determined by taking histological sections 8-10 μ thick (stained in Masson's trichrome) and photographing every fifth section under a magnification of 20x. Eight sections per specimen, corresponding to the central area of the growth plate (in saggital section) were obtained. These images were projected using a photographic enlarger at a 3x linear magnification onto paper. On this paper were a series of six parallel lines at one centimetre intervals. These were aligned with the general axis of the chondrocytes and the boundaries of the growth plate traced. The mean growth plate thickness was calculated by taking the average of the growth plate thicknesses across the six parallel lines and dividing this by the overall magnification (60x).

Flexibility of the sacro-iliac joint (SIJ) was investigated using a modification of the method proposed by Crelin (1955, 1957) to study the changes in SIJ flexibility prior to parturition in mice. In the present experiment, a section of vertebral column with the pelvis attached was placed horizontally against a vertical sheet of X-ray film and radiographed using a horizontal beam. Then the film was replaced and a 50 gm weight suspended from the symphysis pubis of the specimen and a second radiograph taken after 25 seconds load-bearing. The angle between the pelvis and vertebral column subtended at the first sacral vertebra before and after loading was determined trigonometrically (fig 1).

Histological preparations of the growth plates for each group of animals were made at 56d, 70d, 76d 82d and 88d *post partum* and a measure of growth plate thickness made. SIJ flexibility studies were made at 70d, 76d, 82d and 88d *post partum*.

Differences between control and experimental groups in the thickness of the growth plate and in the amount of SIJ flexion were analysed statistically using Student's t-test.

Figure 1 - The trigonometrical determination of the angle between the pelvis and the sacrum (using the half-angle formula (inset)).



Results

The changes in the growth plate thickness and flexion of the SIJ are shown in tables 1 and 2. Figures 2 and 3 represent these results in graphical form. It is evident that during the course of the experiment the growth plate in control animals became progressively thinner. That in animals which had received a 14-day period of undernutrition became statistically thinner than controls by the 70th day but then statistically thicker for the duration of the experiment. In control animals, SIJ flexion declined steadily between the 70th and 88th days *post partum*. Previously undernourished animals showed a smaller (although not statistically significant) flexion at the end of undernutrition followed by increased flexion (being statistically significant at 82d).

Overall pattern in these responses suggests that the changes in growth plate thickness and SIJ flexion occur in concert. This can be seen more clearly when each group's 70d, 76d, 82d and 88d growth plate thicknesses and SIJ flexions are plotted together (figs 4 and 5). Furthermore, plotting each group's growth plate thickness and SIJ flexion against each other (figs 6 and 7) and then superimposing these to produce figures 8 and 9 shows that, when plotted, both the control and experimental groups occupy the same graphical 'state space'.

Visual inspection of the growth plate also suggests that not only are there changes in thickness in the way described above but that there are changes in the shape and number of the chondrocytes too. Although quantitative measures of these were not possible, the point is illustrated in Plate 1. At the end of the period of undernutrition, the growth plate had fewer and flatter chondrocytes by comparison with controls whereas after 12 days realimentation the chondrocytes in previously undernourished animals had become more numerous and more rounded.

Table 1 - Proximal Tibial Epiphyseal Growth Plate Thickness (mm)

Age	Control		Undernourished 56-70 days
56d	0.391 SD 0.016 (2)		- - -
70d	0.348 SD 0.032 (9)	**	0.270 SD 0.062 (10)
76d	0.325 SD 0.019 (9)	**	0.359 SD 0.020 (10)
82d	0.288 SD 0.028 (9)	***	0.358 SD 0.031 (10)
88d	0.276 SD 0.027 (9)	*	0.308 SD 0.026 (10)

Levels of statistical significance:

* 0.05 > p > 0.01

** 0.01 > p > 0.001

*** p < 0.001

Table 2 - Sacro-Iliac Joint Flexion - Change in angle (°)

Age	Control		Undernourished 56-70 days
	-		-
	-		-
	-		-
70d	5.883		4.684
	SD 1.109		SD 1.633
	(7)		(8)
76d	5.740		5.913
	SD 1.194		SD 0.858
	(7)		(8)
82d	4.959	*	6.083
	SD 0.948		SD 0.823
	(7)		(8)
88d	4.743		5.311
	SD 0.701		SD 0.948
	(7)		(8)

Level of statistical significance:

* $0.05 > p > 0.01$

Figure 2 -

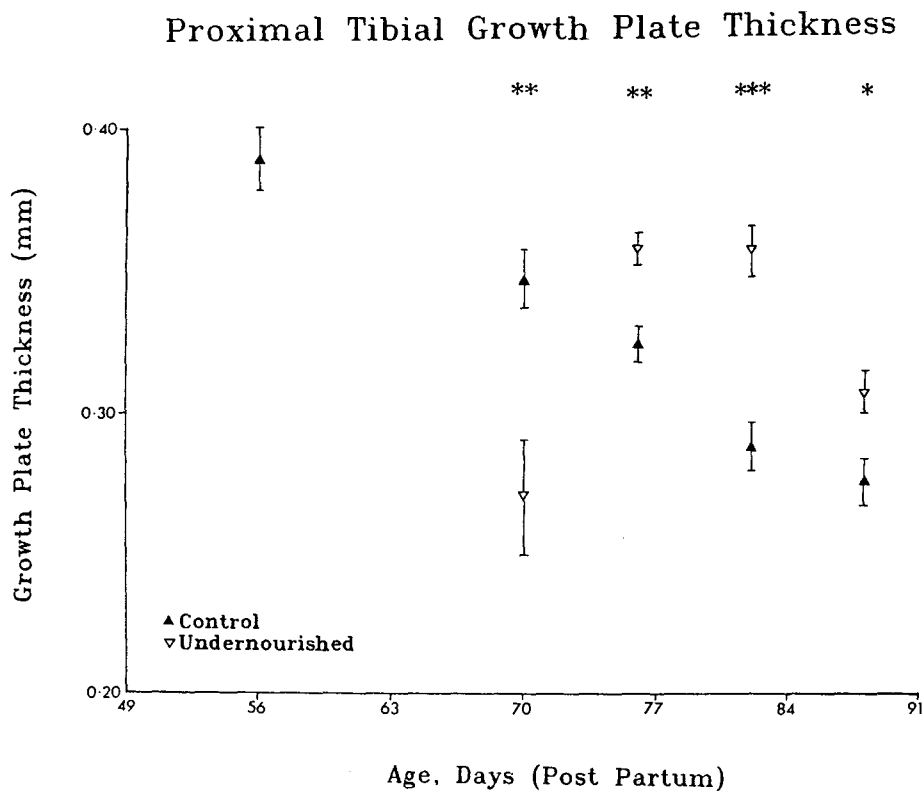


Figure 3 -

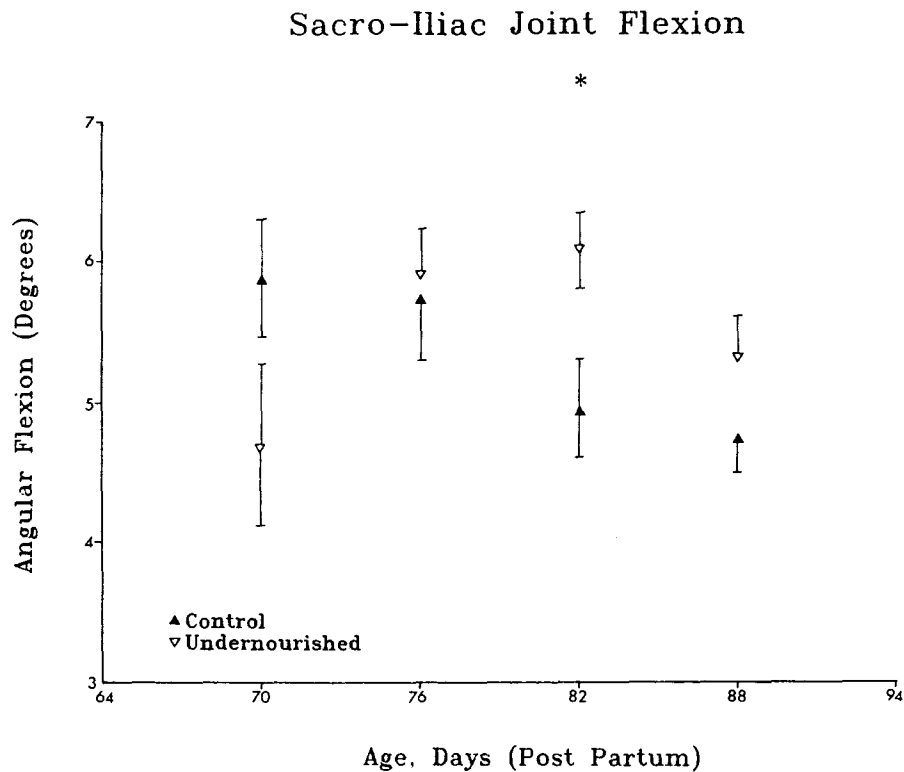


Figure 4 - The relationship of SIJ flexión and proximal tibial growth plate thickness against time. (Control animals.)

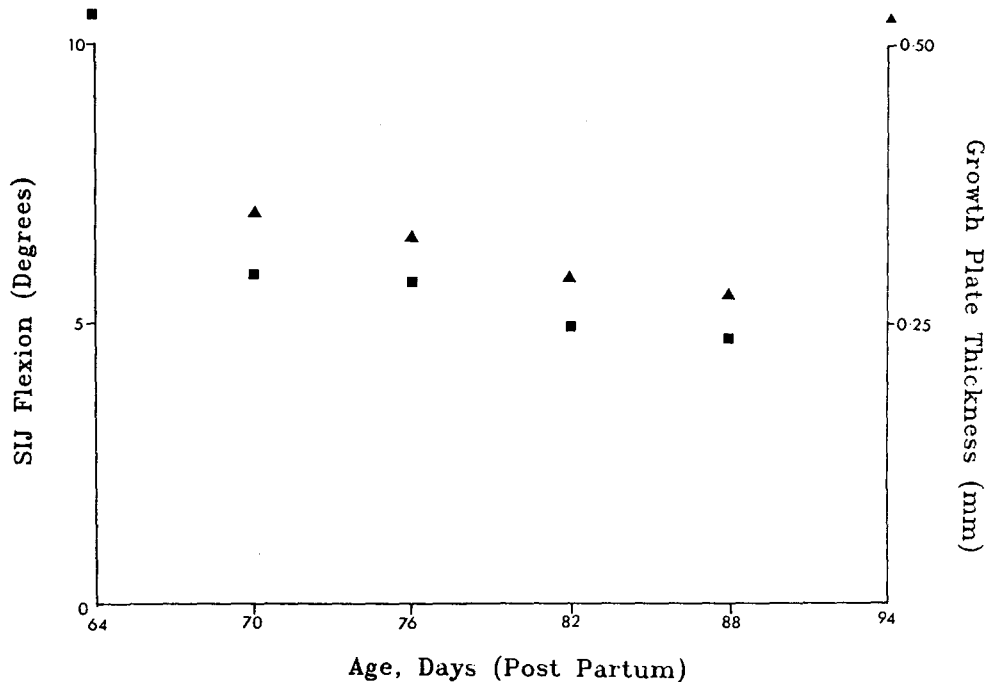


Figure 5 - The relationship of SIJ flexion and proximal tibial growth plate thickness against time. (Experimental animals.)

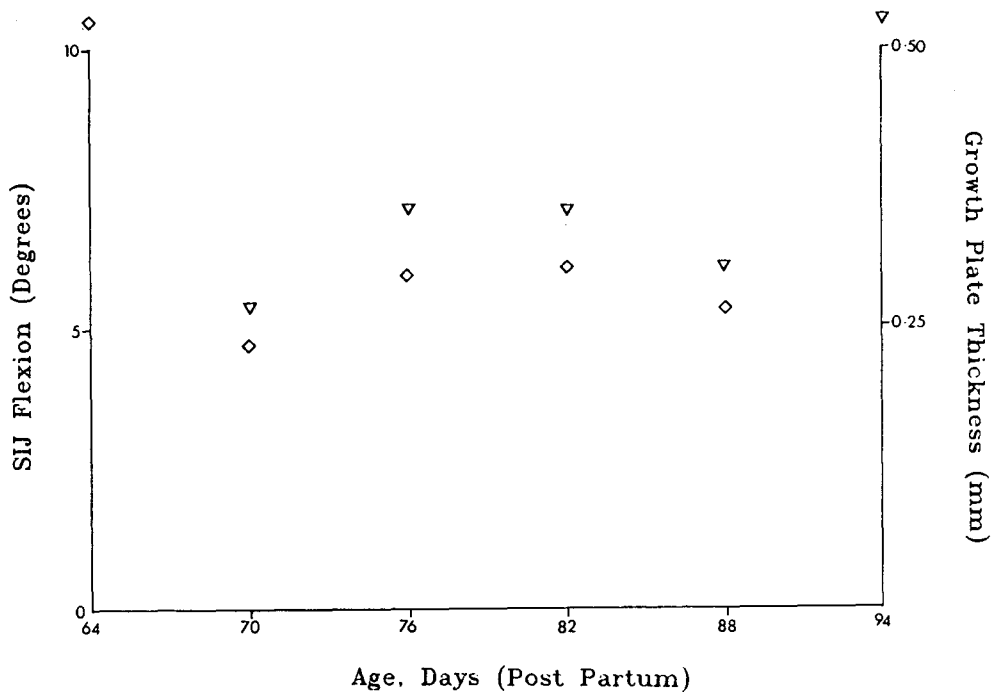


Figure 6 - The state space relationship of SIJ flexion and proximal tibial growth plate thickness. (Control animals.)

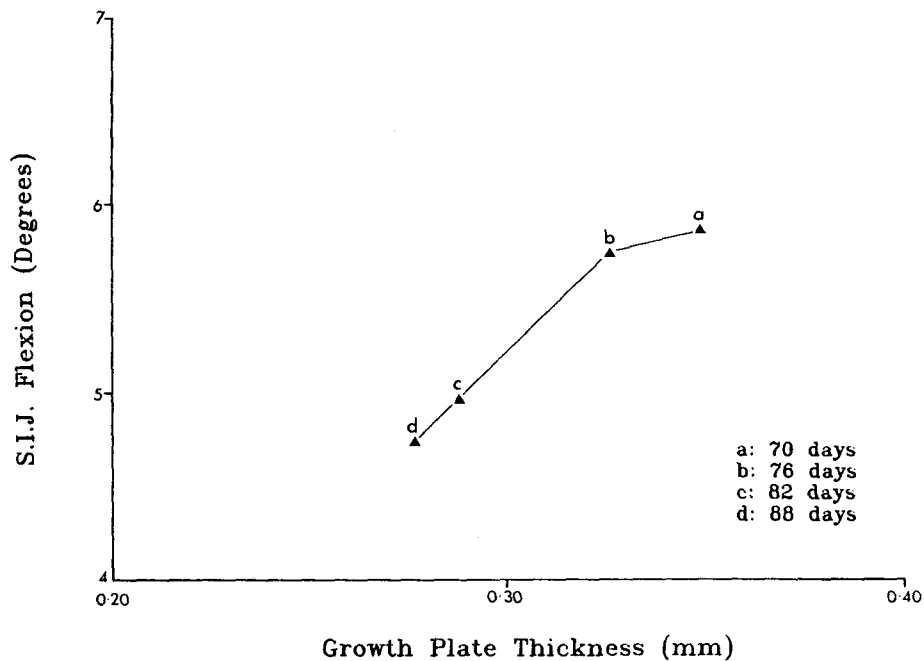


Figure 7 - The state space relationship of SIJ flexion and proximal tibial growth plate thickness. (Experimental animals.)

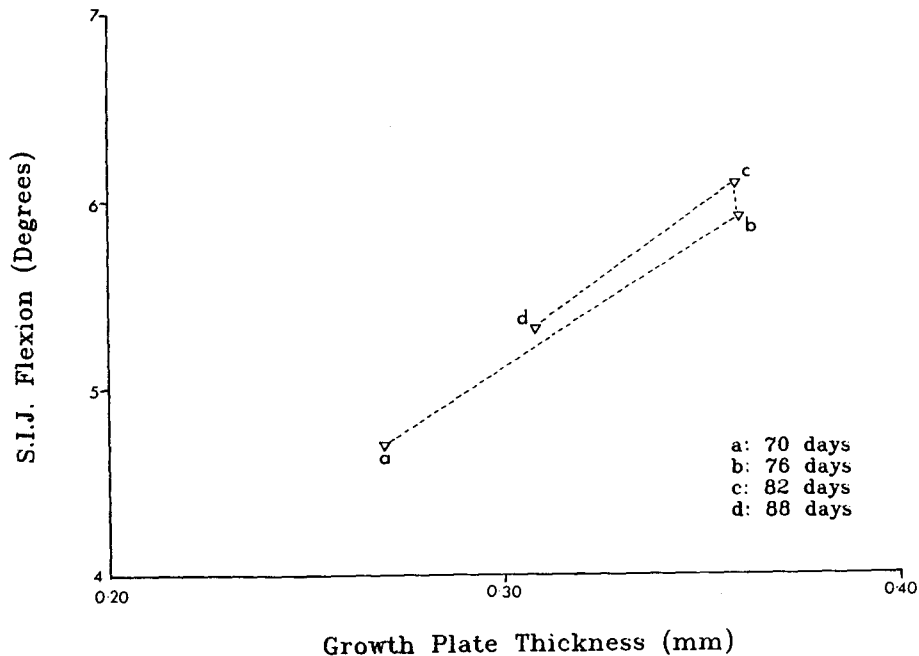


Figure 8 - The state space relationship[†] of SIJ flexion and proximal tibial growth plate thickness. (Control and experimental animals.)

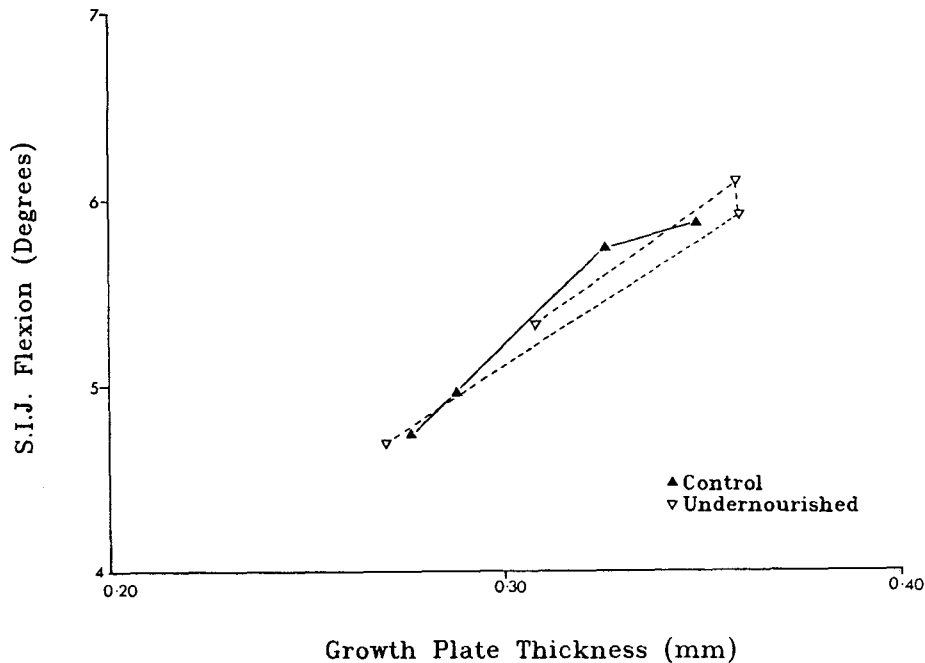


Figure 9 - The state space relationship of SIJ flexion and proximal tibial growth plate thickness. (Control and experimental animals - with Standard Error bars.)

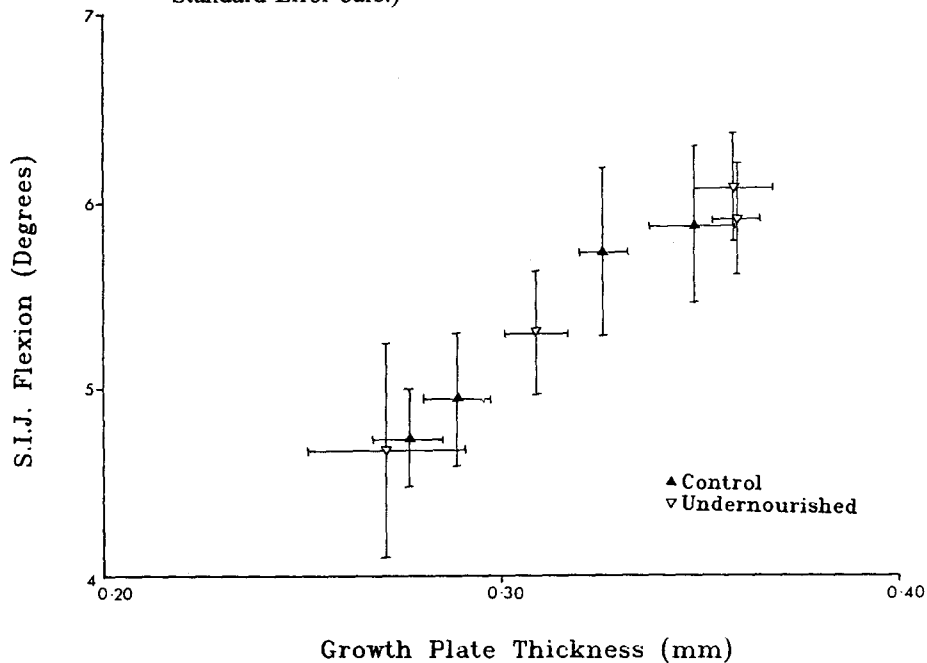
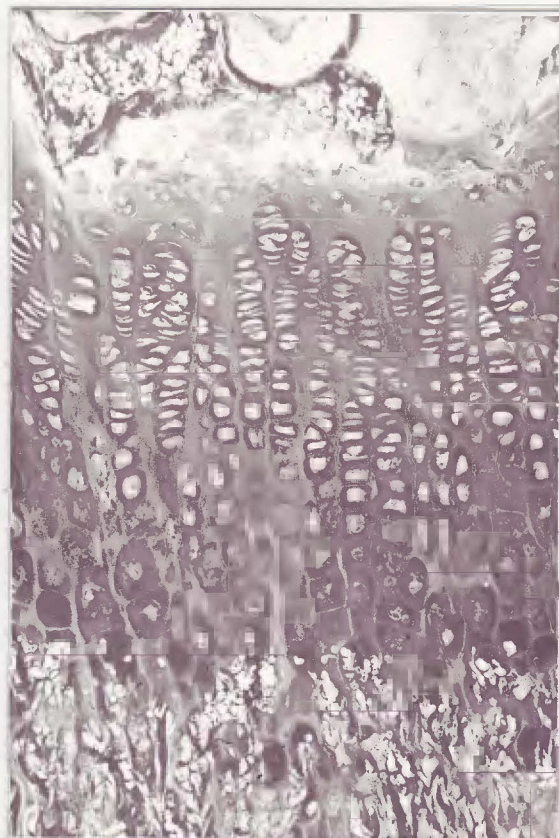
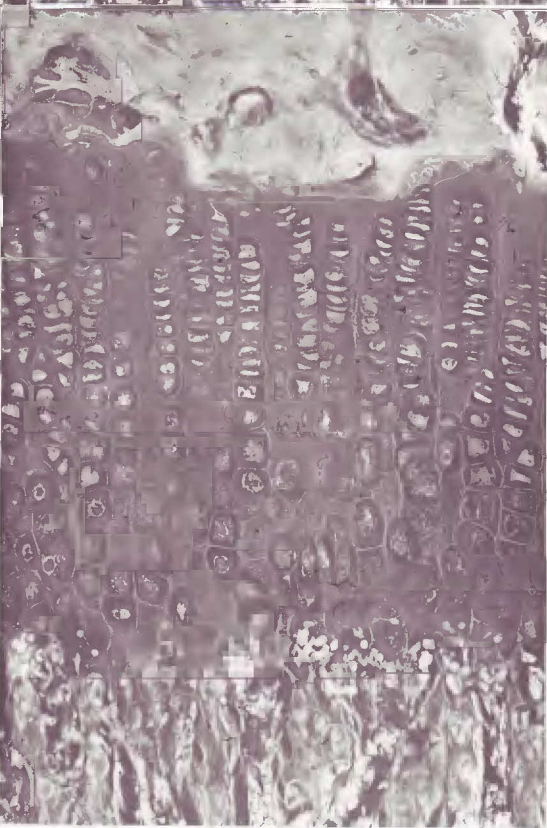
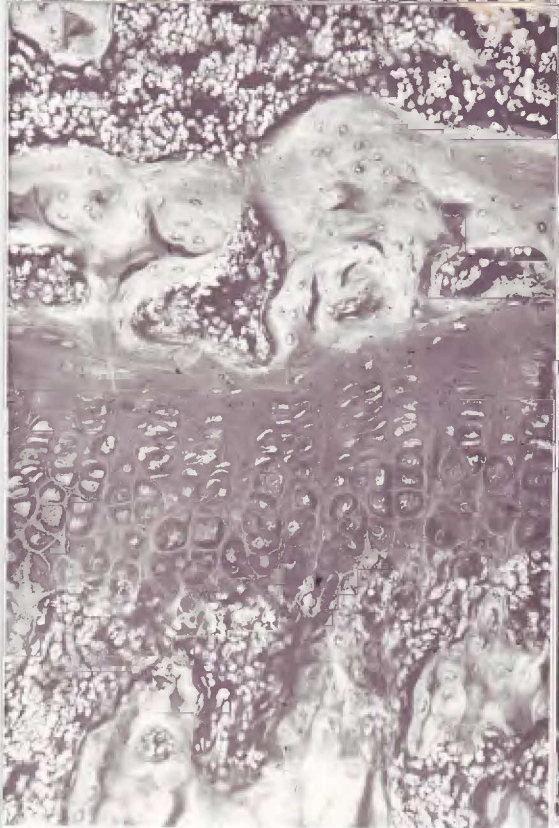
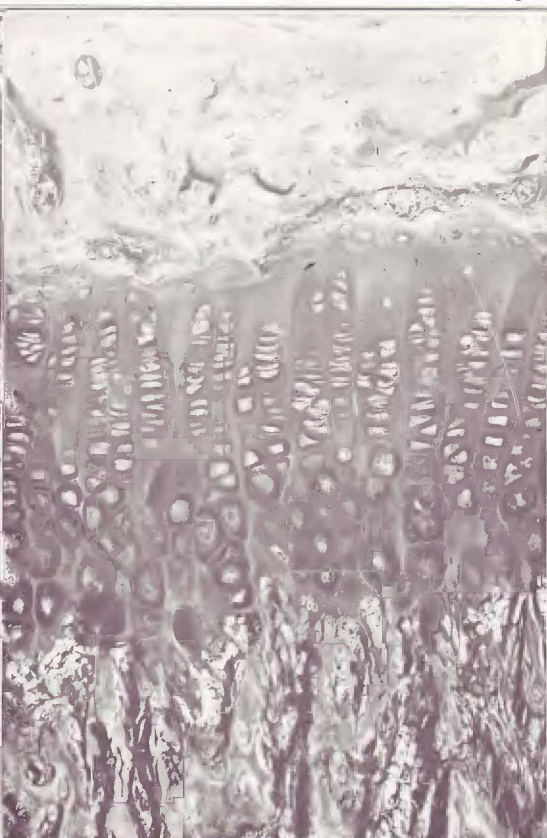


Plate 1 - Photomicrographs of the proximal tibial epiphyseal growth plate.
(Negative print; Masson's Trichrome x189)

Control - 70 days



Control - 82 days



Undernourished - 70 days

Undernourished - 82 days

Discussion

Growth is frequently seen as a process that is, in some way, propelled. In bone growth, the rate of growth in the length of a bone is seen as proportional to the number of chondrocytes within the growth plate and that this number is, in turn, influenced by various blood-borne factors (although clear relationships between such factors and growth rate are still to be shown). Although a faster growing growth plate might be expected to contain more chondrocytes, one would not have expected them to be more rounded than slower growing plates. This is seen when comparing younger, faster-growing animals with older, slower-growing ones and when comparing animals undergoing catch-up growth with controls not undergoing this increased growth rate. One might have expected the chondrocytes stimulated to proliferate in a confined space by the putative blood-borne factors to be those that were more flattened.

Changes in chondrocyte shape have been shown to be under external influence. Crilly (1972) and Ali (1980) have shown that cutting the periosteum of a long bone released mechanical restraint on chondrocytes, thereby increasing growth rate, that is, allowing them to proliferate and to become more rounded. Chondrocytes are normally situated in growth-restricting compartments. The change in the shape of the chondrocytes noticed here is highly suggestive of a release in external restraint on the growth plate rather than a simple increase in chondrocyte proliferation internally.

Changes in SIJ flexion found here suggest that between the 70th and 88th days *post partum*, the connective tissue related to this joint becomes progressively less elastic in control animals. This is in keeping with Moss (1980) who saw the gradual decline in the rate of bone growth as a result of the decline in the elasticity in its associated connective tissue, in particular the periosteum, with age. In previously undernourished animals, changes in SIJ flexion were not linear. SIJ flexion was reduced after undernutrition and increased during the catch-up phase. This suggests that joint changes, presumably mediated by their component connective tissues, occur during normal and catch-up growth.

If this is indicative of connective tissue elasticity change in general, the periosteum may represent a means whereby the growth rate inherent in each growth plate and larger skeletal assemblance is moderated and co-ordinated. (Certainly, Etherington and Bailey (1982) found similar changes occurring in rat skin during undernutrition and catch-up growth.) The site of the 'mechanism' that modulates catch-up growth in the skeleton is perhaps not within the growth plate but outside it. Since all the body's tissues have a connective tissue matrix of some sort, it may not be going too far to suggest that it is via this matrix that the rates of growth (normal, retarded and catch-up) may be influenced.

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